IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Daniel H. Teitelbaum		
Serial No.:	10/798,470	Art Unit:	1614
Filed:	03/11/2004	Examiner:	P.G. Spivack
Entitled:	**Angiotensin Converting Enzyme Inhibitor Use For Treatment And Prevention Of Gastrointestinal Disorders**		

DECLARATION OF DANIEL H. TEITELBAUM UNDER 37 C.F.R. 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: May 8, 2007

By: _____
Jennifer B. Xistris

1. I, Daniel H. Teitelbaum, am one of the co-inventors of record of the subject matter embodied in the above-identified patent application. I am presently employed as Professor of Surgery and the Medical Director for HomeMed and MedEquip at the University of Michigan, the Assignee of the above-identified United States Patent Application.

2. I hereby provide the following comments with regard to the above-identified Patent Application:

The Examiner states that "the teachings of the prior art suggest the claimed subject matter to a person of ordinary skill in the gastroenterology art and reveal a reasonable expectation of success."

However, this is clearly not the case. In this case, the allegation made by the Examiner that angiotensisn converting enzyme (ACE)-inhibitors could treat any inflammatory disease is wrong. In fact, the action of ACE-inhibitors is complex and not intuitive in nature. The activity of these agents appear specific to targeted areas of a mammalian organism. Our own examination (See Spencer et al., Dig Dis Sci. 52: 1060-1070 (2007)) led us to conclude that ACE-inhibitor activity may have to be dependent on the expression of tumor necrosis factor alpha (TNF-α; See Wildhaber et al., Apoptosis, 2005 Dec;10(6):1305-15). TNF-α is a key pro-inflammatory cytokine, and major mediator of inflammatory bowel disease (and also up-regulated during the adaptive phase of short bowel syndrome). We demonstrated in a lengthy series of experiments that ACE inhibition can lead to a down-regulation of TNF-α in the intestinal tract, something which was not obvious, nor previously reported. We also demonstrated that ACE-inhibitor action led to other activities including an increase in intestinal epithelial proliferation, and a significant decline in intestinal epithelial cell apoptosis; both of which are also unique and not previously reported, or speculated upon in the literature. In fact, this line of unique reasoning led the us to test whether ACE-inhibitors could then have efficacy in the adaptation of the bowel during short bowel syndrome and in the reduction in the severity of inflammatory bowel disease. Again, this was a directed line of investigation and reasoning, and certainly nothing intuitive about the manner in which such an investigation was carried out.

There was no way to predict whether an ACE-inhibitor could be used to achieve a reduction in the severity of inflammatory bowel disease when administered to a subject prior to our work.

The mechanism of action of inflammatory conditions varies widely, depending on the precise tissue, organism and period of time (chronic versus acute) of onset of the condition. It is important to emphasize that use of an ACE-inhibitor has a select mode of action which may not act on all tissues, at all times, or for all organisms. The mechanism of action (not ascertainable by Rodgers or Acton) would have to fit perfectly for the type of inflammation. For example, in the case of ACE-inhibitor and inflammatory bowel disease, ACE-inhibitors are able to provide the observed benefits (e.g., reduction in weight loss, improved histological parameters, delay in the onset of heme positive stools and improved colitis score) as described in the patent application when administered to a subject because the ACE-inhibitors reduced the expression of TNF-α; increased intestinal epithelial proliferation, and markedly eliminated intestinal epithelial cell apoptosis (See , Spencer et al., Dig Dis Sci. 2007 Mar 7, epub ahead of print; and Wildhaber et al., Apoptosis, 2005 Dec;10(6):1305-15). Prior to our discoveries, there was nothing in the cited literature that would have otherwise proven or documented the ability of ACE inhibitors to provide the observed benefits.

Additionally, the Examiner's suggestion that the use of ACE-inhibitors as a treatment for inflammatory bowel disease is obvious is refuted by the numerous publications in the literature that show that a tissue or human's response to ACE-inhibitors may be distinctly different, and completely unpredictable. In fact, there are hundreds of reports of ACE-inhibitors resulting in a number of inflammatory processes including angioedema (manifested by an allergic and inflammatory condition of the skin characterized by patches of circumscribed swelling) related to the usage of ACE inhibitors (e.g., Roberts and Wuerz RC (1991) Ann Emerg Med 20:555–558; Maier (1995) Anaesthetist 44:875–879; Vleeming et al., (1998) Drug Safety 18:171–188; Messerli and Nussberger (2000) Lancet 356:608–609). Smoger and Sayed (South Med J, 1998 vol 91:1060-3) reported the onset of mucosal and small bowel angioedema (an inflammatory process within the intestinal mucosa) with the use of captopril (a common ACE-inhibitor). Additionally, tongue ulcerations preceded by loss of taste have been reported as a complication of ACE inhibitor therapy (See Nicholls et al., (1981) Ann Intern Med 94:659). Two cases of long-term usage of ACE inhibitors have also been associated with oral lichen planus (an inflammatory disease affecting the lining of the

mouth (See Firth and Reade (1989) Oral Surg Oral Med Oral Pathol 67:41–44). Thus, it is immediately apparent that ACE-inhibitors cannot be used to provide therapeutically beneficial treatment for inflammatory disease in general.

Additionally, although ACE expression has been seen in the intestine, it was not entirely clear whether a full and competent renin-angiotensin system was present in the intestinal mucosa. In fact, it has previously been reported that the renin-angiotensin system is incomplete in the intestinal mucosa, suggesting that the presence of ACE in the mucosa is solely for digestive purposes, and not for activation of the angiotensin type I or II receptors (See Duggan, et al, Angiotensin receptors and angiotensin I converting enzyme in rat intestine. Am. J. Physiol. 257 (Gastrointest. Liver Physiol. 20): G504-G510, 1989). Prior to experiments performed leading to the present invention, it was not understood whether an intact system existed in the mucosa, making suggestions that ACE-inhibitors might block such a renin-angiotensin system completely non-intuitive. Rather, our work (See Spencer et al., Dig Dis Sci. 52: 1060-1070 (2007)) has demonstrated an intact signaling system, and permitted us to test and characterize whether the blockade of this signaling system with an ACE-inhibitor might have beneficial consequences.

The Rodgers reference does not describe how to use an ACE inhibitor to treat inflammatory bowel disease. Rodgers appears to discuss a method of treating and preventing damage to mucosal tissue using a 3-8 amino acid peptide fragment. Rodgers suggests that the method of treating and preventing damage to mucosal tissue using the peptide fragment of 3-8 amino acids may also be used with other compounds selected from anti-inflammatory drugs, ACE-inhibitors, anti-infectives, growth factors, and antihistamines.

This is a very broad group of agents encompassing agents that both now, and at the time of the present invention, are/were not known to be effective in the treatment of inflammatory bowel disease. The list appears to arbitrarily provide agents that may have anti-inflammatory properties under some conditions, but with absolutely no support for or link to efficacy towards the care of inflammatory bowel disease, short bowel disease or other inflammatory conditions of the intestine.

This leads one to conclude that the suppositions proposed by Rodgers were *not* substantiated by any documented science or experimentation. In fact, our own work finds no support for the use of antihistamines, anti-infectives or growth factors that, as general classes of compounds, each find use in the treatment of inflammatory bowel disease. Further, we find no evidence in Rodgers that demonstrates that ACE-inhibitors could actually provide a treatment for damaged mucosa or for treating inflammatory conditions of the intestine.

Similarly, the Acton patent (U.S. Pat. No. 6,632,830) does not provide any substantiation or documented scientific experiments to support the suppositions that inflammatory bowel diseases might benefit via treatment with an ACE-2 inhibiting compound. Furthermore, we find no evidence in Acton that demonstrates that ACE-inhibitors could actually provide a treatment for damaged mucosa or for treating inflammatory conditions of the intestine.

3. The undersigned declares further that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 3-29-07 By: _____

Daniel H. Teitelbaum, M.D.